REMARKS

Claims 1, 2, 5-9, and 11-18 will be pending on entry of this amendment and response. Claims 1 and 5-8 are amended herein. Support for the claim amendments can be found throughout the application as originally filed, *inter alia*, on page 36, line 34 extending to page 37, line 24; on page 45, lines 8-33; on page 47, line 26 extending to page 48, line 15, in Figure 3A; and in the originally-filed claims. Accordingly, Applicants submit that no new matter has been introduced into the application by way of the instant claim amendments.

Claim 10 was previously cancelled without prejudice or disclaimer as to the subject matter of that claim. Claims 3, 4, 19, and 20 are cancelled herein without prejudice or disclaimer as to the subject matter of the cancelled claims. Applicants respectfully reserve the right to pursue the subject matter of the cancelled claims in one or more continuation or divisional applications.

Interview Summary

In accordance with 37 C.F.R. § 1.133(b) and M.P.E.P. § 713.04, Applicants provide this summary of the interview regarding telephonic correspondence between Examiner Scott Long and Christopher Nichols, Ph.D, on or about May 24 and May 25, 2010. Applicants appreciate the Examiner's statements and have taken them into consideration in the preparation of the present response. It is the understanding of the undersigned representative that an interview was unnecessary as the Examiner expressed an intention to provide a further Office Action after taking the Amendment and Reply filed May 3, 2010 into consideration.

On August 16, 2010, Applicants' undersigned representative telephoned the Examiner seeking clarification of the grounds of rejection provided on page 5. Applicants' representative appreciates the Examiner's time and attention to this item.

Rejections

35 U.S.C. § 103(a)

Claims 1, 3-9, 19, and 20 were rejected under 35 U.S.C. § 103(a), as allegedly rendered obvious by Nagaoka *et al* (Biotech. Lett., 24:1857-62 (2002)("Nagaoka 1")) in view of Nagaoka

et al (Cell Structure and Function, 28(4):327, IP-53 (2003) ("Nagaoka 2")) and further in view of Alonso *et al* (Int. J. Dev. Biol., 389-397 (1991)("Alonso")).[1]

Applicants believe that the rejection has been rendered moot in view of the amendments to the claims.

The claims are amended herein to require, in pertinent part, that the pluripotent stem cells encompassed by the claimed method achieve cell counts at least about two times greater than that achieved by the same pluripotent stem cells cultured on a gelatin plate (i.e., a control plate) after four days.

Under 35 U.S.C. § 103 the Patent Office bears the burden of establishing a *prima facie* case of obviousness. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). There are four separate factual inquiries to consider in making an obviousness determination: (1) the scope and content of the prior art; (2) the level of ordinary skill in the field of the invention; (3) the differences between the claimed invention and the prior art; and (4) the existence of any objective evidence, or "secondary considerations," of non-obviousness. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); *see also* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007).

An "expansive and flexible approach" should be applied when determining obviousness based on a combination of prior art references. KSR, 127 S. Ct. at 1739. However, a claimed invention combining multiple known elements is not rendered obvious simply because each element was known independently in the prior art. Id. at 1741. Rather, a "reason" must be set forth for reaching a *prima facie* obviousness determination. Takeda Chemical Indus., Ltd. v. Alphapharm, 492 F.3d 1350, 1356-1357, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007). In particular, "[i]t remains necessary to show 'some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness,'" Aventis Pharma Deutschland GmbH v. Lupin Ltd., 499 F.3d 1293, 84 USPQ2d 1197, 1204 (Fed. Cir. 2007). Also, modification of a prior art reference may be obvious only if there exists a reason that would have prompted a person of ordinary skill to make the change. KSR, 127 S. Ct. at 1740-41.

[1] In a call by the undersigned representative to Examiner Long on August 16, 2010, it was confirmed that this particular rejection is indeed an obviousness rejection and not an anticipation rejection, as inadvertently indicated on page 5 of the office action.

A. *There is No Reason to Combine the References to Reach the Claimed Invention*

It is purported in the office action that Nagaoka 1 and Nagaoka 2 can be combined with Alonso to reach the claimed invention because Alonso suggests that the F9 embryonal carcinoma cell line can be used as a substitute for embryonic development when studying differentiation. The office action continues by asserting that:

> [i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to culture mammalian embryonic stem cells using the system of Nagaoka. The person of ordinary skill in the art would have been motivated to make that modification to culture mammalian embryonic stem cells using the system of Nagaoka because Nagaoka 2 suggests that the E-cadherin-Fc fusion protein could be used to study embryonic development and a suitable material for studies of mammalian development would be mammalian embryonic stem cells ... An artisan would have expected success, because Nagaoka demonstrates a method of growing pluripotent cells such as F9 mouse teratocarcinoma-derived and embryonal carcinoma cells are known to be useful as a model of embryonic development and are models for embryonic stem cells.

See Office Action, page 9 (emphasis added).

Applicants respectfully traverse. As noted previously, the claims are directed to a method for growing pluripotent stem cells which exhibit a normal karyotype, and are amended herein to require, in pertinent part, that the pluripotent stem cells encompassed by the claimed method achieve cell counts at least about two times greater than that achieved by the same pluripotent stem cells cultured on a gelatin plate (i.e., a control plate) after four days.

Applicants submit that one of ordinary skill in the art would have had no reason to combine the cited references in order to reach the claimed invention. Applicants submit that Nagaoka 1 is directed to the evaluation of the differentiation of primary hepatocytes. According to Nagaoka 1, hepatocytes adhered to the E-cad-Fc coated surface by a homophilic interaction of E-cadherins and showed differentiated phenotypes such as low DNA synthesizing activity and maintenance of tryptophan oxygenase expression. *See* Nagaoka 1, Abstract. The office action cites to page 1860, col. 1, of Nagaoka 1 for the teaching of growing F9 teratocarcinoma cells in a liquid medium and in a culturing vessel having a E-cad-IgG Fc coated surface. *See* office action, page 5. Applicants submit that the only reference at this citation directed to F9 cells states: "[f]urthermore, the F9 teratocarcinoma cells, which undergo E-cadherin-mediated cell aggregation, adhered to E-cad-Fc-coated surface (data not shown)." *See* Nagaoka 1, p. 1860, col.

1. Applicants submit that Nagaoka 1 does not present data on the proliferation potency of F9 cells on E-cad-Fc plates, and does not teach or suggest the use of pluripotent stem cells in a method of growing pluripotent stem cells to certain cell densities over time. In fact, Nagaoka 1 cautions that "[e]-Cadherin mediated cell-cell adhesion has a potentiality at the very least to inhibit proliferation and possibly to promote differentiation." *See* Nagaoka 1, page 1861, 1st col. (emphasis added).

Nagaoka 2 states that E-cad-Fc plates were generated to clarify the function of E-cadherin in the developmental process, and that "F9 mouse teratocarcinoma-derived embryonal carcinoma cell line was used as a useful model system for the study of embryonic development." *See* Nagaoka 2 (emphasis added). As with Nagaoka 1, Applicants submit that Nagaoka 2 does not present data on the proliferation potency of F9 cells on E-cad-Fc plates, and does not teach or suggest the use of pluripotent stem cells in a method of growing pluripotent stem cells to certain cell densities over time. Instead, Nagaoka 2 reports effects of certain types of culture plates on the ability of F9 cells to form colonies.

The office action cites to Alonso for the suggestion that Alonso may be combined with Nagaoka 1 and Nagaoka 2 to reach the claimed invention because the "... F9 embryonal carcinoma cell line can be used as a substitute for embryonic stem cells when studying differentiation." *See* office action, page 6 (emphasis added). Alonso does not teach that F9 cells are model cells for the proliferation potency of pluripotent stem cells. The office action further states that "Alonso et al. suggest that 'EC cells are the stem cells of teratocarcinomas' (page 390, parag. 2), thereby suggesting that embryonic stem cells and F9 can be substituted for each other in various culturing methods." *See* office action, page 9. Further in the cited paragraph, Alonso states that "[t]he F9 cell line is characterized by the inability to differentiate spontaneously, and is therefore a so-called nullipotent cell line." *See* Alonso, page 390, 1st col. Applicants submit that this inability of the F9 cell line is a property distinct from those of ES cells and rebuts a suggestion that F9 and ES cells can be substituted for each other.

Because Alonso does not cure the deficiencies of Nagaoka 1 and Nagaoka 2, Applicants submit that one of ordinary skill in the art would not have had a reason to combine the cited references for the purpose of attempting to reach the claimed invention. This is because the claimed invention is directed to a method of growing pluripotent stem cells, and the cited

references (collectively and individually) are silent to the proliferation potency of F9 cells or pluripotent stem cells on E-cad-Fc plates.

B. One of Ordinary Skill in the Art Would Not Have Had a Reasonable Expectation of Success in Achieving the Claimed Invention

Applicants submit that one of ordinary skill in the art would not have had a reasonable expectation of success in achieving the claimed invention, even if there had been a reason to combine the references. There is no teaching or suggestion in the cited references that pluripotent stem cells would show enhanced proliferation potency when grown on E-cad-Fc plates, when compared to the same cells grown on gelatin plates. As noted previously, Nagaoka 1 cautions one of ordinary skill in the art that "E-cadherin mediated cell-cell adhesion has a potentiality at the very least to inhibit proliferation ...". *See* Nagaoka 1, p. 1860, col. 1 (emphasis added). Applicants submit that this teaching suggests to one of ordinary skill in the art that they would not have an expectation of success in obtaining enhanced proliferation potency when culturing F9 cells or pluripotent stem cells on E-cad-Fc plates, and teaches away from the claimed invention. Thus, according to Nagaoka 1, one of ordinary skill in the art should expect the inhibition of proliferation when using E-cad-Fc plates.

Neither Nagaoka 2 nor Alonso rebuts this cautionary teaching. Accordingly, Applicants submit that one of ordinary skill in the art would not have had a reasonable expectation of success in achieving the claimed invention.

C. Experimental Results in the Specification Support Applicants' Position

In Example 3, the proliferation potency of ES cells on an E-cad-Fc plate was evaluated. Two pluripotent stem cell lines (i.e., 500 murine ES EB3 cells and 500 murine ES R1 cells, respectively) were seeded on E-cad-Fc plates or gelatin plates and cultured for 3 to 4 days. After rinsing the cells with serum-free medium, the cell counts were measured with Alamar Blue as described in Example 2 of the specification. The results demonstrated that the:

> ... number of ES cells cultured on the E-cad-Fc plate with respect to the number of ES cells cultured on the gelatin plate by day 3 of culturing was significantly higher for both the EB3 and R1 cells lines (see FIG. 3A). Also, the cell counts of the E-cad-Fc plate groups with both ES cell lines were approximately 2 times greater by day 4 of culturing ...

See Specification, page 47, line 34 extending to page 48, line 3. By contrast, "[w]hen the same experiment was conducted with F9 cells, no difference was found in the cell proliferation potencies of the E-cad-Fc plate cultured group and the ordinary plate cultured group." *See* Specification, page 48, line 12-15 (emphasis added).

Accordingly, Applicants submit that the claimed invention is not obvious over Nagaoka 1 in view of Nagaoka 2 and further in view of Alonso, and respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) as it applies to claims 1, 5-9, and 20.

35 U.S.C. § 102(b)

Claims 1, 3, and 9 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by the disclosure of Xu *et al* (Nature Biotechnology, 19:971-974 (2001)("Xu")).

Applicants believe that the rejection has been rendered moot in view of the amendments to the claims.

As stated in MPEP § 2131, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Without acquiescing in the merits of the rejection, Applicants have amended claim 1 to recite in pertinent part that the culturing vessel includes immobilized or coated on a substrate solid phase surface a molecule belonging to the cadherin family. Applicants submit that Xu fails to teach this element of claim 1 (and the dependent claims), and therefore fails to anticipate the claims as amended herein. Applicants further submit that the amended claims are not rendered obvious at least for the reasons provided previously.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, and 9 under 35 U.S.C. § 102(b).

Conclusion

An indication of allowance of all claims is earnestly solicited. Early notification of a favorable consideration is respectfully requested.

Respectfully submitted,

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Dated: September 21, 2010

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